Regenerative medicine – Glossary

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Summary of pages
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Foreword

Publishing information

This Publicly Available Specification (PAS) has been commissioned by the UK Department for Innovation, Universities and Skills (DIUS) and developed through the British Standards Institution (BSI). It came into effect on 30 April 2008.

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This PAS is not to be regarded as a British Standard. It will be withdrawn upon publication of its content in, or as, a British Standard.

The PAS process enables a specification to be rapidly developed in order to fulfil an immediate need in industry. A PAS may be considered for further development as a British Standard, or constitute part of the UK input into the development of a European or International Standard.

Relationship with other publications

This glossary provides a set of terms and definitions that support and build on the terminology in PAS 83, Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics – from basic research to clinical application.

Where possible, an attempt has been made to use terms and definitions that have been defined in existing standards, in particular ASTM F2312-04, Standard terminology relating to tissue engineered medicinal products.
A number of regulations exist that are relevant to the field of regenerative medicine. These regulations contain terms that are defined in some detail. In some instances regulatory definitions have been included verbatim. However, in order for this glossary to achieve its intended objective, more succinct and precise definitions consistent with regulations have been developed.

**Presentational conventions**

The terms in this glossary are arranged by topic. Where a term and its definition is relevant to more than one topic, to avoid duplication it has not been reproduced under each topic.

Notes are provided throughout the text of this standard. Notes give references and additional information.

**Contractual and legal considerations**

Attention is drawn to the following statutory regulations.

a) Human Tissue Act 2004 [1].

b) European Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [2].

c) Human Fertilisation and Embryology Act 1990 [3].


This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

**Compliance with a Publicly Available Specification cannot confer immunity from legal obligations.**

This Publicly Available Specification is not to be regarded as a British Standard.
Introduction

This Publicly Available Specification (PAS) has been developed to encourage the use of common terms and definitions within the field of regenerative medicine. For the purpose of this PAS regenerative medicine:

*replaces or regenerates cells, tissues or organs, to restore or establish normal function.*

There has been increasing scrutiny of current standardization and regulations by researchers, manufacturers and the general public as cell-based therapeutics move nearer to commercialization. As an initial response, the former Department of Trade and Industry (DTI) commissioned BSI to produce PAS 83, *Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics* which outlined the key stages in product development and was published in November 2006.

UK stakeholders also identified a need for further standardization to achieve consensus on the terms and definitions used within regenerative medicine. Using the views and opinions of key UK stakeholders, this PAS has been developed to meet this need and act as an accompanying document to PAS 83.

The aim of this PAS is to provide clear guidance on the meaning of terminology currently used within this field in the UK by industry, regulators, government and academia. Where applicable, terms and definitions have been aligned with existing regulations, codes of practice or standards. The sources of reproduced or adapted terms and definitions are referenced within this PAS.

It is recognized that there may be international differences in terminology in current use, such as between the US and Europe and particularly with regard to regional legislation. In this case, the European legislative or common terms have been used where possible.

It is intended that this document will help UK stakeholders to:

- prepare for legal, commercial and societal issues;
- facilitate a common understanding of the science of regenerative medicine;
- improve communication and understanding of advances in the field;
- demonstrate best practice and product quality;
- reduce research, development, production and transaction costs.
1 Scope

This Publicly Available Specification lists terms and definitions:

a) associated with the naming of types of regenerative medicine products and therapies;

b) that describe materials, processes, methodologies and applications within regenerative medicine.

It covers:

i) general terms (see Clause 2);

ii) cell and tissue components (Clause 3)

iii) non-cellular components (see Clause 4);

iv) cell and tissue procurement (see Clause 5);

v) measurement and analysis (see Clause 6);

vi) manufacturing and production (see Clause 7);

vii) clinical trials (see Clause 8 and Table A.1);

viii) regulatory terms for products and therapies (see Table A.2).

2 General

2.1 allogeneic

where donor and recipient are different individuals

[derived from PAS 83:2006]

2.2 allograft

allogeneic graft

NOTE 1  Also called homograft.

NOTE 2  This definition differs from ASTM F2312-04.

2.3 apoptosis

programmed cell death

NOTE  See necrosis (definition 2.7).

2.4 autograft

autologous graft

NOTE  This definition differs from ASTM F2312-04.

2.5 autologous

where donor and recipient are the same individual

[PAS 83:2006]

2.6 bioaesthetics

regenerative medicine-like therapies aimed at cosmesis rather than traditional medical alignments
2.7 cancer vaccine
specific therapy intended either to treat existing cancers or to prevent
the development of cancer

NOTE 1 Also called immunotherapeutic product.
NOTE 2 A cancer vaccine that treats existing cancers is called a
therapeutic vaccine and includes live cell therapies.
NOTE 3 A cancer vaccine that prevents the development of cancer is
called a prophylactic vaccine and includes live cell therapies.
[derived from the National Cancer Institute Cancer Vaccine Fact
Sheet [12]]

2.8 cell based medicinal product (CBMP)
medicinal product containing cells

NOTE These products may be combined with non-cellular components
and may include genetically modified human cells.
[derived from the European Medicines Agency’s Guideline on Human
Cell-Based Medicinal Products [13]]

2.9 cell culture
in vitro growth and maintenance of cells

2.10 cell therapy
administration of cells to the body to the benefit of the recipient

2.11 cloning
production of identical copies of a cell or organism

NOTE This can be conducted via somatic cell nuclear transfer
(definition 3.43).

2.12 cosmesis
preservation, restoration or bestowing of bodily beauty

[Dorland’s Pocket Medical Dictionary [14]]

2.13 drug substance
substance or mixture of substances intended to be used in the
manufacture of a drug (medicinal) product and that, when used in the
production of a drug, becomes an active ingredient of the drug product

NOTE 1 Such substances are intended to furnish pharmacological
activity or other direct effect in the diagnosis, cure, mitigation, treatment
or prevention of disease or to affect the structure and function of the body.
NOTE 2 Also known as active substance and active pharmaceutical
ingredient (API).
NOTE 3 See intermediate (definition 2.25).
[derived from ICH Harmonised Tripartite Guideline Q7 [15]]

2.14 ex vivo
outside the living body

2.15 extracorporeal
situated or occurring outside the body

2.16 gene therapy
deliberate introduction of genetic material into cells

NOTE Attention is drawn to the definition in European Regulation
2.17 genotype  
genetic constitution of an individual cell or organism

2.18 heterologous use  
different use

2.19 heterotopic  
different anatomical location

2.20 homologous use  
same use

2.21 homotopic  
same anatomical location

  NOTE Also called orthotopic.

2.22 in vitro  
within an artificial environment

2.23 in vivo  
within the living body

2.24 informed consent  
voluntary consent given by an individual to participate in a study after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule

  NOTE A legal definition applicable in the UK is given in Table A.1.

[derived from the UK Stem Cell Bank’s Code of Practice for the Use of Human Stem Cell Lines [16]]

2.25 intermediate  
material produced during steps of the processing of a drug substance that undergoes further molecular change or purification before it becomes a drug substance

  NOTE 1 Intermediates may or may not be isolated.

  NOTE 2 See drug substance (definition 2.13).

[derived from the European Commission’s EudraLex: Rules governing medicinal products in the European Union [17]]

2.26 minimal manipulation  
processing that does not alter the relevant biological characteristics of cells or tissue

  NOTE See substantial manipulation (definition 2.41).

[derived from the US Code of Federal Regulations, 21CFR1271.3(f)(2) [18]]

2.27 necrosis  
non programmed cell death

2.28 organ  
structurally and functionally distinct part of the human body, formed by different tissues, that maintains its structure, vascularization and capacity to develop physiological functions with an important level of autonomy

2.29 **passage**
transfer of cells from one culture environment to another

2.30 **passage number**
number of times cells have been transferred from one culture environment to another

2.31 **phenotype**
physical and biological characteristics of a cell or organism as determined by both genetic make-up and environmental influences

2.32 **plating efficiency**
measure of the number of colonies originating from single cells

2.33 **population doubling**
measured doubling of cell numbers

[Medicines and Healthcare products Regulatory Agency, *A Code of Practice for the Production of Human-derived Therapeutic Products* [19]]

2.34 **products**
goods or services associated with regenerative medicine

*NOTE* This includes therapies.

2.35 **raw material**
starting materials, reagents and solvents intended for use in the production of intermediates or a drug substance

[derived from the European Commission’s *EudraLex: Rules governing medicinal products in the European Union* [17]]

2.36 **regen**
industry that develops and sells regenerative medicine products

[Regenerative Medicine, 2007, 2(5), 753–756 [20]]

2.37 **regenerative medicine**
replaces or regenerates human cells, tissues or organs to restore or establish normal function

[Regenerative Medicine, 2008, 3(1), 1–5 [21]]

2.38 **reproductive cloning**
production of identical animals via cloning

*NOTE* See cloning (definition 2.11).

[derived from the Stem Cell Information Glossary [22]]

2.39 **seeding density**
amount of cells to be applied for a given application

*NOTE* Usually expressed as total number of cells per unit area or volume.

2.40 **senescence**
decline or degeneration related to cellular aging
2.41 **substantial manipulation**
manipulation of cells or tissue so that biological characteristics, physiological functions or structural properties relevant for the therapeutic application are achieved
[derived from European Directive 2004/27/EC [8]]

2.42 **syngeneic**
where donor and recipient are genetically identical individuals

*NOTE* For example, identical twins or animals of a single highly inbred strain.

2.43 **therapeutic cloning**
production of cells that exactly match the cells of a donor

2.44 **therapy**
treatment intended to heal or relieve a disorder

2.45 **tissue**
aggregation of specialized cells united in the performance of a particular set of functions
[derived from ASTM F2312-04]

2.46 **tissue engineering**
use of a combination of cells, engineering, materials and methods to manufacture ex vivo living tissues and organs that can be implanted to improve or replace biological functions

*NOTE* Usually through the use of scaffolds for restoration or regeneration of tissues or organs.

2.47 **transplantation**
process of implanting cells, tissues or organs
[derived from ASTM F2312-04]

2.48 **xenogeneic**
where the donor and recipient belong to different species
[ASTM F2312-04]

2.49 **xenograft**
xenogeneic graft

*NOTE* This definition differs from ASTM F2312-04.

### 3 Cell and tissue components

3.1 **admixed embryo**
embryo that contains both human and animal material

*NOTE* An example of this includes a cytoplasmic hybrid embryo (cybrid) (definition 3.15).

3.2 **adult stem cell**
stem cell derived from the early embryo (beyond the blastocyst stage), fetus and adult body that is multipotent rather than pluripotent

*NOTE* Also known as somatic stem cell.
[derived from the UK Stem Cell Bank’s *Code of Practice for the Use of Human Stem Cell Lines* [16]]
3.3 adventitious
coming from an external source

3.4 blastocyst
pre-implantation embryo of about 150 cells produced by cell division following fertilization

*NOTE* The blastocyst is a sphere made up of an outer layer of cells (the trophoblast) and a cluster of cells on the interior (the inner cell mass).

[derived from the Stem Cell Information Glossary [22]]

3.5 cell expansion
increase in the number of cells by their replication

[Medicines and Healthcare products Regulatory Agency, *A Code of Practice for the Production of Human-derived Therapeutic Products* [19]]

3.6 cell line
characterized cell culture that has been demonstrated to be phenotypically and genotypically consistent over a specified number of population doublings

[derived from Medicines and Healthcare products Regulatory Agency, *A Code of Practice for the Production of Human-derived Therapeutic Products* [19]]

3.7 cell migration
movement of cells in response to a stimulus

3.8 contaminant
foreign material, organism or impurity

3.9 continuous cell line
cell line that appears to have the capacity for indefinite replication

[Medicines and Healthcare products Regulatory Agency, *A Code of Practice for the Production of Human-derived Therapeutic Products* [19]]

3.10 cord blood stem cell
stem cell isolated from the umbilical cord blood at birth

3.11 cryopreservation
maintenance of the viability of cells, tissues and organs by the process of controlled cooling and storing at very low temperatures and subsequent re-warming

*NOTE* See vitrification (definition 3.46).

3.12 cryoprotectant
agent used to protect cells, tissues and organs from damage that can occur during cryopreservation

*NOTE* An example of damage is intracellular ice crystal formation.

3.13 culture medium
nutrient supply used to support the growth and expansion of cells or to maintain tissue or organ cultures

3.14 cytokine
intercellular signalling protein or peptide
3.15 **cytoplasmic hybrid embryos (cybrid)**
embryo produced by replacing the nucleus of an animal egg or a cell
derived from an animal embryo with a human cell or the nucleus of a
human cell

*NOTE*  This is an example of an admixed embryo (definition 3.1).

3.16 **de-differentiation**
regression of a cell to a less mature phenotype

3.17 **defined medium**
culture medium in which all components are known

3.18 **differentiation**
development of a cell to a more mature phenotype

3.19 **embryonic stem cell**
undifferentiated cell derived from a pre-blastocyst or blastocyst that is
both immortal and pluripotent
[derived from the Stem Cell Information Glossary [22]]

3.20 **embryonic stem cell line**
embryonic stem cells that have been cultured under in vitro conditions
that allow proliferation without differentiation
[derived from the Stem Cell Information Glossary [22]]

3.21 **extracellular matrix (ECM)**
on-cellular matrix surrounding cells

3.22 **feeder cell**
cell used in co-culture to sustain the viability and desired characteristics
of other cells

3.23 **fetal stem cell**
stem cell originating from the fetus that has the potential to make a
limited range of specialized cell types

3.24 **finite cell line**
cell line that can be maintained for a limited number of population
doublings before it becomes senescent and ultimately loses the ability
to replicate
Practice for the Production of Human-derived Therapeutic
Products* [19]]

3.25 **haematopoiesis**
formation of blood from haematopoietic stem cells

3.26 **haematopoietic stem cells (HSC)**
stem cells that gives rise to all red and white blood cells and platelets
[derived from the Stem Cell Information Glossary [22]]

3.27 **immortal**
capacity of cells to proliferate indefinitely

3.28 **induced pluripotent stem (IPS) cells**
human embryonic stem cell-like cells that are produced by
de-differentiating adult cells
3.29 **inner cell mass (ICM)**
cluster of cells inside the blastocyst

*NOTE*  These cells are used to generate embryonic stem cells (definition 3.19).

[derived from the Stem Cell Information Glossary [22]]

3.30 **major histocompatibility complex**
member of a family of polymorphic genes encoding proteins that regulate immune responses

3.31 **marrow stromal cell**
differentiated progeny from mesenchymal stem cells

*NOTE*  Typically a heterogenous population including a range of stromal cells at different stages of differentiation and of different composition or nature including osteoblasts (bone), chondrocytes (cartilage) and adipocytes (fat).

3.32 **mesenchymal stem cell**
multipotent bone marrow-derived non-hematopoietic stem cells with the capacity to generate cells of the stromal lineage

*NOTE 1*  Examples include osteoblasts (bone), chondrocytes (cartilage) and adipocytes (fat).

*NOTE 2*  The name is contentious and these cells are also referred to as skeletal stem cells or bone marrow stromal fibroblastic stem cells.

3.33 **multipotent**
having the ability to develop into a limited number of cell types

3.34 **mycoplasma**
organism of the phylum Mollicutes

*NOTE*  These are resistant to many antibiotics, are a common contaminant in cell culture and can cause serious deleterious effect on cells.

3.35 **nullipotent**
having the ability to develop into only one cell type

3.36 **pathogen**
disease-producing agent or microorganism

[Dorland’s Pocket Medical Dictionary [14]]

3.37 **pluripotent**
having the ability to develop into all types of cell, except extraembryonic tissues

*NOTE*  An example of extraembryonic tissues is placenta.

[derived from the Stem Cell Information Glossary [22]]

3.38 **precursor cell**
cell at an intermediate stage of development

3.39 **primary cell culture**
culture of cells isolated directly from tissue

3.40 **somatic stem cell**
see adult stem cell (definition 3.2)

3.41 **stromal cells**
non haematopoietic stem cells derived from blood organs, which are capable of supporting the growth of blood cells

*NOTE*  Bone marrow is an example of a blood organ.

[derived from the Stem Cell Information Glossary [22]]
3.42 **stem cell**
cell capable of asymmetric division, proliferation and provision of cells that can differentiate

3.43 **somatic cell nuclear transfer (SCNT)**
technique that combines an enucleated egg (nucleus removed) and the nucleus of a somatic cell to make an embryo

3.44 **totipotent**
having the ability to develop into all types of cell including extraembryonic tissues

*NOTE An example of extraembryonic tissues is placenta.*

3.45 **trophoblast**
extraembryonic tissue that forms the placenta
[derived from the Stem Cell Information Glossary [22]]

3.46 **vitrification**
form of cryopreservation whereby cells, tissues or organs are converted into a glass-like amorphous state prior to cooling to ultra-low temperatures

4 **Non-cellular components**

4.1 **bioactive agent**
agent that has a biological effect on cells or tissue

[derived from PAS 83:2006]

4.2 **biomaterial**
material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body

[BS EN ISO 10993-6:2007, definition 3.3]

4.3 **excipient**
ingredient added intentionally to a drug substance, which does not have pharmacological properties in the quantity used

[derived from ICH Harmonised Tripartite Guideline Q1A(R2) [23]]

4.4 **growth factor**
naturally occurring protein capable of stimulating cellular proliferation

4.5 **scaffold**
support, delivery vehicle or matrix for facilitating the migration, binding or transport of cells or bioactive agents

[derived from ASTM F2312-04]

5 **Cell and tissue procurement**

5.1 **cell bank**
collection of containers storing cells of uniform composition under defined conditions

[derived from ICH Harmonised Tripartite Guideline Q5D [24]]

5.2 **current Good Clinical Practice (cGCP)**
regulations, codes and guidelines covering the conduct of clinical research studies

[derived from PAS 83:2006]
5.3 donation
process of obtaining human tissues or cells with informed consent

NOTE See informed consent (definition 2.24).

5.4 provenance
adequate knowledge of the source of a material, cells or reagents used in the derivation of cells in order for a risk assessment of contamination or infection to be made

NOTE 1 Provenance is essential when a material, cells or reagents are intended for clinical use.

NOTE 2 Provenance can include knowledge of the medical histories of donors of gametes used to derive embryos.

5.5 serious adverse event
untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or that might result in, or prolong, hospitalization or morbidity

[Human Tissue Authority, Code of Practice 1 – Consent [25]]

5.6 tissue bank
collection of characterized tissues for clinical utility

5.7 tissue establishment
establishment where the activities of processing, preservation, storage or distribution of human tissue and cells are undertaken

NOTE 1 For example, a tissue bank or a unit of a hospital.

NOTE 2 It might also be responsible for procurement or testing of tissue and cells.


5.8 traceability
ability to account for the whereabouts of donated tissues or cells and their status at all points from initial collection right through to either transplantation or disposal

6 Measurement and analysis

6.1 cell authenticity
degree to which a population of cells has the correct identity and is free of other cell types

NOTE The quality of the authentication depends on the specificity and sensitivity of the technique used.

6.2 biocompatibility
ability of a material to perform with an appropriate host response in a specific application

[The Williams Dictionary of Biomaterials [26]]

6.3 biomarker
molecular indicator of a specific biological property

6.4 cell morphology
microscopic study of the form and structure of cells

6.5 cell viability
measure of a cell’s potential for metabolism or multiplication
6.6 **comparative genomic hybridization (CGH)**
method for the analysis of copy number changes in the chromosomal DNA content of a cell or tissue

6.7 **contamination**
unintended presence of a cell or a material with another cell or material

[ASTM F2312-04]

6.8 **current Good Cell Culture Practice (cGCCP)**
guidelines to define minimum standards in cell and tissue culture

[PAS 83:2006]

6.9 **DNA profiling**
technique that uses DNA samples to distinguish between two individuals or samples of the same species

*NOTE* Also called DNA fingerprinting.

6.10 **epigenetic**
heritable change in the pattern of gene expression that is mediated by mechanisms other than alterations in the primary nucleotide sequence of a gene

*NOTE* For example, DNA methylation or histone modifications.

[derived from *Epigenetic mechanisms of gene regulation* [27]]

6.11 **gene expression profile (transcriptome)**
spectrum of mRNA levels resulting from gene activity at a given time

6.12 **flow cytometry**
technique that measures and analyses multiple physical characteristics of single cells as they flow in a fluid stream through a beam of light

6.13 **fluorescence activated cell sorting (FACS)**
sorting of a heterogeneous mixture of cells into two or more containers, one cell at a time, using the specific light scattering and fluorescent characteristics of each cell

*NOTE* See magnetic activated cell sorting (MACS) (definition 6.21).

[derived from *The Williams Dictionary of Biomaterials* [26]]

6.14 **haemocytometer**
glass slide with a chamber for counting cells in a given volume

6.15 **histocompatibility**
measure of the extent to which implanted cells are immunologically matched to the recipient

6.16 **histology**
microscopic study of the form and structure of tissues

6.17 **immunocytochemistry**
method that uses antibodies to identify, locate and visualize specific molecules in single cells

6.18 **immunohistochemistry**
method that uses antibodies to identify, locate and visualize specific molecules in tissue sections

6.19 **impurity**
component present in a medicinal product that is not the desired product or a product related substance
6.20 **karyotyping**
Assessment of the complete set of all chromosomes of a cell to identify any chromosomal abnormalities

[PAS 83:2006]

6.21 **magnetic activated cell sorting (MACS)**
Sorting of a heterogeneous mixture of cells via mixing with magnetic beads coated with antibodies against specific cell surface antigens, followed by separation and selection using a column placed in a magnetic field

6.22 **microarray**
Set of DNA or protein molecules spotted onto a solid matrix for use in multiplex probing of a biological sample to determine gene or protein expression, marker pattern or the nucleotide sequence of DNA/RNA

6.23 **polymerase chain reaction (PCR)**
Technique for the in vitro amplification of a specific target DNA sequence from a background of non-target DNA

6.24 **porosity**
Property of a solid which contains an inherent or induced network of channels and open spaces characterized by the ratio of pore (void) volume to the apparent (total) volume of a porous material

*NOTE* This is commonly expressed as a percentage.

[ASTM F2312-04]

6.25 **protein expression**
Translation and post-translational processing of proteins

6.26 **purity**
Level of freedom from contamination

6.27 **safety**
Freedom from unacceptable risk


6.28 **surface marker**
Molecule that binds to a cell surface receptor and is used to identify cell type

*NOTE* This is usually an antibody.

6.29 **tissue typing**
Process of determining the allelic types of the antigens of the major histocompatibility complex that determine the acceptance or rejection of a tissue graft

6.30 **toxicology**
Study of the potential of materials to give rise to harm to health by virtue of their effect on biological systems

[ASTM F2312-04]

6.31 **tumour**
Swelling of a part of the body caused by an abnormal growth of tissue whether benign or malignant

6.32 **tumourigenicity**
Tendency of cells to form a tumour
7 Manufacturing and production

7.1 aseptic
manner of handling or processing to minimize microbiological contamination

7.2 batch (or lot)
defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous
[derived from the European Commission’s Eudralex: Rules governing medicinal products in the European Union [28]]

7.3 bioprocessing
activity performed on cells, tissues and organs other than collection
NOTE For example, preparation and preservation for storage and packaging.
[ASTM F2312-04]

7.4 bioreactor
device, equipment or apparatus designed to contain structures, both cellular and molecular, that are capable of taking part in a specific biological process and from which the products of the process can be harvested or extracted
[The Williams Dictionary of Biomaterials [26]]

7.5 cleanroom (or clean facility)
room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary
[BS EN ISO 14644-1:1996, definition 2.1.1]

7.6 cost benefit analysis
form of economic evaluation which attempts to value the consequences of a therapy in monetary terms in order to ascertain whether the beneficial consequences of the programme justify the costs
[derived from Methods for the Economic Evaluation of Health Care Programmes [29]]

7.7 current Good Laboratory Practice (cGLP)
regulations, codes and guidelines for laboratories conducting non-clinical studies
[PAS 83:2006]

7.8 current Good Manufacturing Practice (cGMP)
set of regulations, codes and guidelines for the manufacture of regenerative medicine therapies, medicinal products, medical devices, diagnostic products, food products and active pharmaceutical ingredients
[derived from PAS 83:2006]

7.9 current Good Tissue Practice (cGTP)
set of regulations, codes and guidelines for the manufacture of cell-based therapeutic products
[PAS 83:2006]
7.10 **dose**
prescribed quantity of a medicine or of a remedial agent

[Larousse Dictionary of Science and Technology [30]]

7.11 **in-process control**
checks performed during processing in order to monitor and if necessary adjust the process to ensure that the product conforms to its specification

*NOTE 1* The environment or equipment may be included as part of in-process control.

*NOTE 2* One element of in-process control is process analytical technology (PAT) (definition 7.18).

[Medicines and Healthcare products Regulatory Agency, A Code of Practice for the Production of Human-derived Therapeutic Products [19]]

7.12 **investigational medicinal product (IMP)**
pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial

*NOTE* This includes products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

[derived from European Directive 2001/20/EC [31]]

7.13 **manufacture**
any or all of the steps in the procurement, screening, testing, processing, storage, labelling, packaging or distribution of any human cellular or tissue-based product

[ASTM F2312-04]

7.14 **marketing authorization**
authorization by a European regulatory authority for a medicinal product to be placed on the market

7.15 **post market surveillance**
practice of monitoring the safety or efficacy of a medicinal product or device after it has been released onto the market

7.16 **potency**
quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties

[ICH Harmonised Tripartite Guideline Q6B [32]]

7.17 **preservation**
prevention or retardation of the biological or physical deterioration of cells or tissues

*NOTE 1* This can be achieved during cell or tissue processing, for example, through the use of chemical agents or alterations in environmental conditions.

*NOTE 2* See cryopreservation (definition 3.11).

7.18 **process analytical technology (PAT)**

system for designing, analysing and controlling manufacturing through timely measurements, during processing, of critical quality and performance attributes of raw and in-process materials, and processes with the goal of ensuring final product quality

[ICH Harmonised Tripartite Guideline Q8 [33]]

7.19 **processing**

activity involved in the manufacture of products

*NOTE* See bioprocessing (definition 7.3).

[ASTM F2312-04]

7.20 **qualification**

confirmation by examination and provision of objective evidence that equipment functions in the manner intended by the manufacturer

*NOTE* See validation (definition 7.38).

7.21 **qualified person (QP)**

person responsible for certifying that a batch of medicinal product conforms to requirements prior to release


7.22 **qualified person responsible for pharmacovigilance (QPPV)**

person responsible for pharmacovigilance for licensed medicinal products


7.23 **quality**

degree to which a set of inherent properties of a product, system or process fulfils requirements

[ICH Harmonised Tripartite Guideline Q9 [34]]

7.24 **quality assurance (QA)**

total sum of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use

[derived from European Commission’s Eudralex: Rules governing medicinal products in the European Union [35]]

7.25 **quality control (QC)**

process or set of processes or measures used to maintain predefined standards to assure the quality of a product

[derived from PAS 83:2006]

7.26 **quality system**

organizational structure, defined responsibilities, procedures, processes and resources for implementing quality management including all activities which contribute to quality, directly or indirectly

[European Directive 2006/17/EC [36]]
7.27 **release criteria**
set of measurements taken to determine fitness for product release

*NOTE*  These measurements can include identity, purity, impurities, sterility, potency, cell viability and total cell number.

[derived from the European Medicines Agency’s Guideline on Human Cell-Based Medicinal Products [13]]

7.28 **risk**
combination of the probability of occurrence of harm and the severity of that harm


7.29 **risk analysis**
systematic use of available information to identify hazards and to estimate the risks

*NOTE*  Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.


7.30 **risk management**
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk

[BS EN ISO 14971:2007, definition 2.22]

7.31 **scale out (or scale horizontally)**
increasing production by an increase in the number of units rather than increasing the size of the process

7.32 **scale up (or scale vertically)**
increasing the size of the process rather than increasing production by an increase in the number of units

7.33 **specification**
set of criteria to which a medicinal product should conform to be considered acceptable for its intended use

[ICH Harmonised Tripartite Guideline Q6B [32]]

7.34 **stability testing**
determination of the shelf life under storage and in-use for a finished product and its intermediates

*NOTE*  For example, assessment of the ability of cells to survive and maintain the phenotype and genotype needed for the intended function.

[derived from the European Medicines Agency’s Guideline on Human Cell-Based Medicinal Products [13]]

7.35 **standard operating procedure (SOP)**
detailed, written instructions to achieve uniformity of the performance of a specific function

[ICH Harmonised Tripartite Guideline E6 [37]]

7.36 **sterile**
free from bacteria or other living microorganisms

*NOTE*  Sterility includes the absence of all microbiological life, such as fungi, bacteria or viruses.

7.37 **translation**
active turning of a basic science discovery into a safe and effective therapy deployed in routine clinical practice
7.38 **validation**
establishment of documented evidence which provides a high degree of
assurance that a planned process will consistently perform according to
the intended specified outcomes

*NOTE* Also know as process validation.

Practice for the Production of Human-derived Therapeutic
Products* [19]]

7.39 **whole bioprocessing**

<allogeneic> entire bioprocess from donor through to implantation of
a cell or tissue engineering therapy

<autologous> entire bioprocess from patient biopsy through to
implantation of a cell or tissue engineering therapy

8 **Clinical trials**

8.1 **adverse event**
untoward medical occurrence in a patient, or clinical trial subject, who
has been administered a medicinal product and which is not necessarily
caused by the product

*NOTE* An adverse event can also be defined by severity or whether it is
expected, e.g. serious adverse event or serious unexpected adverse event.

[derived from European Directive 2001/20/EC [31]]

8.2 **adverse event reporting**
system for notification to a regulatory authority of adverse events

8.3 **adverse reaction**
untoward and unintended responses to an investigational medicinal
product related to any dose administered

*NOTE* An adverse reaction can also be defined by severity or whether it is
expected, e.g. serious adverse reaction or suspected unexpected serious
adverse reaction (SUSAR).

[derived from European Directive 2001/20/EC [31]]

8.4 **arm**
treatment or patient group in a randomized trial

8.5 **baseline**
information gathered at the beginning of a study from which variations
found in the study are measured

8.6 **chief investigator**
investigator who takes overall charge of a multi centre study

*NOTE* See clinical investigator (definition 8.7) and principal
investigator (definition 8.30).

8.7 **clinical investigator**
medical researcher who carries out a clinical trial’s protocol

*NOTE* See chief investigator (definition 8.6) and principal investigator
(definition 8.30).

8.8 **clinical translation**
process of taking a treatment from the laboratory to testing in
volunteers
8.9 **clinical trial**
investigation in human subjects intended to discover or verify the safety and efficacy of a therapy

*NOTE A legal definition applicable in the UK is given in Table A.1.*

8.10 **control**
benchmark against which experimental observations are evaluated

8.11 **dose finding study**
study in which different groups of patients are given different doses of a product to select the best doses for use in later, larger scale trials

8.12 **double blind study**
randomized trial in which the clinician and patient are unaware of which arm of the trial the patient is on

8.13 **eligibility criteria (or inclusion and exclusion criteria)**
predetermined criteria determining whether an individual may or may not be allowed to enter a clinical trial

8.14 **endpoint**
overall outcome that the protocol is designed to evaluate

8.15 **ethics committee**
independent body consisting of healthcare professionals and non medical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial or study

*NOTE 1 A legal definition applicable in the UK is given in Table A.1.*

*NOTE 2 A hierarchy of ethical committees exist. The committees are known as the local research ethics committee (LREC), the multi centre research ethics committee (MREC) and the central office for research ethics committee (COREC).*

8.16 **immunorejection**
failure of a recipient’s body to accept a transplanted tissue or organ as the result of immunological incompatibility

8.17 **immunosuppression**
suppression of the immune response, as by drugs or radiation, in order to prevent the rejection of grafts or transplants or control autoimmune diseases

8.18 **minimum effect dose**
minimum dose that achieves clinical efficacy

8.19 **non-clinical study**
study performed in vitro and/or in vivo (in animals) to provide data to support initiation of clinical phase studies and/or support marketing authorization

*NOTE Also called preclinical study.*

8.20 **pharmacodynamics**
study of the biochemical and physiological effects of medicinal products and the mechanisms of their actions

[Dorland’s Pocket Medical Dictionary [14]]
8.21 **pharmacokinetics**
study of the fate of drugs in a body

*NOTE* This includes a mathematical account of their absorption, distribution, metabolism and excretion.

[derived from the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment’s *Annual Report 2006* [38]]

8.22 **pharmacology**
study of the uses, effects and actions of medicinal products on living systems

8.23 **pharmacovigilance**
science relating to the detection, assessment, understanding and prevention of adverse effects

*NOTE* This is particularly concerned with the long term and short term side effects of medicines.

[derived from the World Health Organization’s *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products* [39]]

8.24 **phase 0 trial**
clinical study whereby a single sub-therapeutic dose is administered to volunteers to gather pharmacological data

*NOTE* Also known as microdosing.

8.25 **phase I/II trial**
clinical study performed in patients to determine safety and preliminary efficacy data

*NOTE* Conventional pharmaceutical phase I trials have not been defined because they are generally not applicable to regenerative medicine therapies because of the ethics of administering live cells to healthy volunteers.

8.26 **phase II trial**
clinical study to ascertain efficacy and safety for a regenerative medicine therapy

8.27 **phase III trial**
clinical study that involves a large number of patients in different clinical settings to determine safety and efficacy

[derived from the US Department of Health and Human Services’ *Protecting Human Research Subjects: Institutional Review Board (IRB) Guidebook* [40]]

8.28 **phase IV trial**
post authorization clinical studies on medicinal products

8.29 **placebo controlled study**
comparative clinical trial in which the control is a product or treatment with no therapeutic effect

8.30 **principle investigator**
investigator who takes overall charge at a clinical trial centre

*NOTE* See chief investigator (definition 8.6) and clinical investigator (definition 8.7).
8.31 **protocol**
document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial

*NOTE*  The term protocol refers to the protocol, successive versions of the protocol and protocol amendments.

[derived from European Directive 2001/20/EC [31]]

8.32 **randomized trial**
study in which participants are randomly (i.e. by chance) assigned to one of two or more treatment arms of a clinical trial

8.33 **sham procedure**
procedure that is performed as a control and that is similar to but omits a key therapeutic element of the treatment or procedure under investigation

8.34 **side effect**
undesired action or effect resulting from therapeutic treatment

8.35 **single blind**
randomized trial in which either the clinician or patient are unaware of which arm of the trial the patient is on

8.36 **subject**
individual who participates in a clinical trial as either a recipient of the investigational medicinal product or control

[derived from European Directive 2001/20/EC [31]]
## Annex A (informative)  Regulatory terms

### Table A.1  Regulatory terms for clinical trials

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Legislation</th>
</tr>
</thead>
<tbody>
<tr>
<td>clinical trial</td>
<td>investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy</td>
<td>European Directive 2001/20/EC [31]</td>
</tr>
<tr>
<td>ethics committee</td>
<td>independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent</td>
<td>European Directive 2001/20/EC [31]</td>
</tr>
<tr>
<td>informed consent</td>
<td>decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation</td>
<td>European Directive 2001/20/EC [31]</td>
</tr>
</tbody>
</table>
Table A.2  Regulatory terms for products and therapies

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Legislation</th>
</tr>
</thead>
<tbody>
<tr>
<td>active implantable medical device</td>
<td>active medical device that is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure</td>
<td>European Directive 90/385/EEC [41]</td>
</tr>
<tr>
<td>active medical device</td>
<td>medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity</td>
<td>European Directive 90/385/EEC [41]</td>
</tr>
<tr>
<td>combined advanced therapy medicinal product</td>
<td>product that incorporates one or more medical devices or one or more active implantable medical devices its cellular or tissue part contains viable cells or tissues or its cellular or tissue part containing non-viable cells or tissues is liable to act upon the human body with action that can be considered as primary to that of the devices referred to</td>
<td>European Regulation No. 1394/2007 [10] amending European Directive 2001/83/EC [4] and European Regulation No. 726/2004 [11]</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
<td>Legislation</td>
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<tr>
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</tbody>
</table>
| engineered cells and tissues             | cells or tissues that have been subjected to substantial manipulation, so that the biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; and that are not intended to be used for the same essential function or functions in the recipient as in the donor  

**NOTE** The following manipulations are not considered as substantial manipulations:  
- cutting;  
- grinding;  
- shaping;  
- centrifugation;  
- soaking in antibiotic or antimicrobial solutions;  
- sterilization;  
- irradiation;  
- cell separation, concentration or purification;  
- filtering;  
- lyophilization;  
- freezing;  
- cryopreservation;  
<p>| medical device                            | instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means | European Directive 2007/47/EC [42] amending European Directive 93/42/EEC [43]                      |
| medicinal product                         | substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis                                                                                      | European Directive 2004/27/EC [8]                                                                   |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Legislation</th>
</tr>
</thead>
</table>
| somatic cell therapy medicinal product    | use in humans of autologous, allogeneic or xenogenic somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect through metabolic, pharmacological and immunological means.  
*NOTE*  This manipulation includes the expansion or activation of autologous cell populations  
| tissue engineered product                 | product that contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue | European Regulation No. 1394/2007 [10] amending European Directive 2001/83/EC [4] and European Regulation No. 726/2004 [11] |
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Standards publications

For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ASTM F2312-04, Standard terminology relating to tissue engineered medicinal products

BS EN ISO 10993-6:2007, Biological evaluation of medical devices – Part 6: Tests for local effects after implantation

BS EN ISO 14971:2007, Medical devices – Application of risk management to medical devices

BS EN ISO 14644-1:1996, Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness

PAS 83:2006, Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics – From basic research to clinical application


Other publications


**Useful websites**

- EU pharmaceutical information
  http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
- EU legislation information
- European Medicines Agency (EMEA)
  www.emea.eu.int
- UK Medicines and Healthcare products Regulatory Agency (MHRA)
  www.mhra.gov.uk
- UK Department of Health
  www.dh.gov.uk
• UK Department of Health/Medical Research Council online clinical trials guide
  www.ct-toolkit.ac.uk
• UK Human Fertilisation and Embryology Authority
  www.hfea.gov.uk
• UK Human Tissue Authority
  www.hta.gov.uk
• UK National Blood Service
  www.blood.co.uk
• UK Stem Cell Bank
  www.ukstemcellbank.org.uk
• US Food and Drug Administration
  www.fda.gov
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